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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,431	10/08/2003	Keith A. Moore	XANO / 33	7143

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WOOD, HERRON & EVANS, LLP
2700 CAREW TOWER
441 VINE STREET
CINCINNATI, OH 45202

EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1617	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/681,431	MOORE ET AL.	
	Examiner	Art Unit	
	Umamaheswari Ramachandran	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-38* is/are pending in the application.

4a) Of the above claim(s) *25-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 10-24, 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 1/16/2007. Claims 1, 6, 8, 11, 13, 15, 17, 19, 21, 23 have been amended, claim 9 has been canceled and Claims 25-37 have been withdrawn and 38 has been added new. Claims 1-8, 10-24, 38 are currently pending.

Applicants' response to the rejection of claims 1-25 under 35 U.S.C 112 (1) is found persuasive and the rejection is withdrawn. Applicants' amendment of the claims and the response to the rejection of claims 5-6, 8, 9-10, 25 under 35 U.S.C 112 (2) have been considered and found persuasive and the rejection is withdrawn. Applicant's amendment to claims 1, 6, 8, 11, 13, 15, 17, 19, 21, 23 and the addition of new claim 38 necessitated the following new rejections.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Morel et al. (Psychopharmacology, 1987, 92, 68-72).

Morel et al. teaches the administration of N-desmethyl levomepromazine (NDM-LMP) in a pharmaceutically acceptable formulation (p 69, col. 2, Drugs and metabolites) to rats. The reference teaches that NDM-LMP has similar potency to that of levomepromazine (LMP) in dopamine D2 receptor binding (p 71, lines 45-47) contributing to a certain extent to the antipsychotic effects of LMP. The reference also teaches that NDM-LMP had significant muscle relaxant or sedative activity in mice (Fig 1). The reference teaches a dose of 5.5 mg/Kg for ED_{50} (dose that produces half

maximal response) and for example a patient weighing 50 kg would be administered 550 mg for maximum response.

Claims 11-12, 15-20, 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Hals et al. (Life Sciences, 43, 405-412, 1988).

Hals et al. teaches the in vitro binding affinity of NDM-LMP for dopamine (D2), adrenergic (α1, α2), muscarinic and histamine (H1) receptors (Table 2, p 610, Fig 1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 3, 6, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morel et al. (Psychopharmacology, 1987, 92, 68-72) as applied to claims 1, 4 above and in view of Jacob et al. (U.S. 2,837,518) and further in view of Breton et al. (U.S. 6,344,461).

Morel et al's teachings discussed as above.

The reference does not teach the administration of NDM-LMP to a patient to achieve antiemetic effect or analgesic effect.

Jacob et al. teaches that NDM-LMP, a phenothiazine derivative has a marked activity on the central nervous system by virtue of which they are of general use as potentiators of general anesthetics and analgesics, antiemetics and neuroleptics. The reference teaches that in comparison with known compounds having such activity, the

compound such as NDM-LMP exhibit more favorable relationship between therapeutic and secondary effects. (Col. 1, lines 30-63).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer NDM-LMP to achieve antiemetic and analgesic effects. The motivation to do is taught by Jacob et al. The reference teaches that in comparison with known compounds having such activity, the compound such as NDM-LMP exhibit more favorable relationship between therapeutic and secondary effects.

Morel and Jacob specifically do not teach a concentration of NDM-LMP to achieve specific effects such as antiemetic, antiprutic effect or an analgesic or to control symptoms of BPH with a lower concentration of NDM-LMP than a formulation of NDM-LMP as claimed in claim 6.

Morel teaches a dose of NDM-LMP that produces half maximal response when administered to rats for sedative effects. It would have been obvious to one of ordinary skill in the art at the time of invention to adjust the dose range of NDM-LMP by routine experimentation to achieve the desired effects.

The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." I*n re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re*

Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Morel and Jacob do not teach the administration of NDM-LMP to provide ion channel antagonist effect.

Breton et al. teaches that phenothiazine compounds are calmodulin antagonists and in turn are calcium channel inhibitors (col. 4, lines 30-46).

It would have been obvious to one of ordinary skill in the art to administer NDM-LMP to provide ion-channel antagonist effect. The motivation to do is provided by Breton et al. The reference teaches that calmodulin antagonist such as phenothiazine are active inside the cell and have an effect on the release of the intracellular calcium reserves or on inhibition of the formation of the calcium/calmodulin complex (col. 4, lines 40-43). Hence it would have been obvious to one of ordinary skill in the art to administer a phenothiazine compound and in particular NDM-LMP because Jacob teaches NDM-LMP as a phenothiazine derivative and one would expect to achieve similar success or superior results in administering NDM-LMP to provide ion channel antagonist effects as Breton teaches phenothiazine as a calcium channel blocker.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Morel et al. (Psychopharmacology, 1987, 92, 68-72) as applied to claims 1, 4 above and in view of Hals et al. (Life Sciences, 43, 405-412, 1988) as applied to claims 11-12, 15-20, 38 above and further in view of Molina et al. (Eur J of Pharmacology, 455, 2002, 59-64).

Morel et al. and Hals et al's teachings discussed as above.

Morel and Hals do not teach the antihypertensive effect upon administration of NDM-LMP.

Molina et al. teaches that alpha1 adrenergic receptor antagonist such as NAN-190 induced hypotension.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer NDM-LMP to provide antihypertensive effect. The motivation to do is provided by Molina et al. Hals et al. teaches that NDM-LMP is an alpha adrenergic antagonist and Molina teaches that alpha1 adrenergic receptor antagonist induced hypotension in an anesthetized adult rat. Hence it would have been obvious to one of ordinary skill in the art at the time of the invention to administer NDM-LMP as it is an alpha 1 adrenergic receptor antagonist and one can expect similar success or superior results to induce antihypertensive effect.

Claims 5, 8, 10,13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morel et al. (Psychopharmacology, 1987, 92, 68-72) as applied to claims 1, 4 above in view of Dahl et al. (Psychopharmacology, 1981, 74, 101-104) and further in view of Twycross et al. (Preg Paliat Care 1997, 5, 2, 49-53).

Morel et al's teachings discussed as above. Morel teaches a dose of LMP and NDM-LMP that produces half maximal response when administered to rats.

The reference does not teach administering NDM-LMP to a patient to produce substantially the same pharmaceutical effects as LMP at a dose effective to achieve

substantially the same steady state serum concentration as achieved by LMP as combined LMP and NDM-LMP serum concentration.

Dahl et al. teaches the administration of LMP to psychiatric patients and further teaches that its metabolite NDM-LMP had 71% of the potency of LMP in the dopamine receptor binding test and had 80% potency in the α1 adrenergic binding (p 102, col.2, Results) and the sulfoxide metabolite lacks neuroleptic potency (see Abstract). The reference also teaches that NDM-LMP is pharmacologically active and NDM-LMP may contribute to the antipsychotic effects. The reference further teaches that NDM-LMP is found in higher plasma concentrations than the parent drug in patients.

It would have been obvious to one of ordinary skill in the art at the time of invention to adjust the dose range of NDM-LMP by routine experimentation to achieve the same pharmaceutical effects as that of LMP and to achieve desired serum concentrations. Dahl teaches the administration of LMP to patients and teaches the potency of its main metabolite NDM-LMP. The reference further teaches that NDM-LMP is pharmacologically active and may contribute to the antipsychotic effects. Hence it would have been obvious to one of ordinary skill in the art to achieve dosages of NDM-LMP at desired ranges to achieve the same pharmaceutical effects as that of LMP by routine experimentation.

The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." I*n re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330,

65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Dahl teaches that sulfoxide metabolite of LMP lacks neuroleptic potency. Hence when LMP is administered the pharmaceutical effects of the drug are reduced due to the drug being metabolized to sulfoxide. But upon administration of NDM-LMP there is no sulfoxide metabolite formation and hence the pharmaceutical effects of NDM-LMP is not altered. This addresses claim 10.

Morel et al. and Dahl et al. do not teach the administration of NDM-LMP to provide serotonergic antagonist effects by NDM-LMP binding to serotonin receptor.

Twycross et al. teaches that levomepromazine is a potent antagonist of serotonin (5HT) receptors (see Abstract).

It would have been obvious to one of ordinary skill in the art to administer NDM-LMP to provide serotonergic antagonist effects. The motivation to do so is taught by Dahl et al. and Twycross et al. Dahl teaches that NDM-LMP is found in higher plasma concentrations than the parent drug in patients. Twycross teaches that levomepromazine is a potent antagonist of serotonin (5HT) receptors. Hence it would have been obvious to one of ordinary skill in the art to administer NDM-LMP for LMP to

provide serotonergic antagonist effects because Dahl teaches that NDM-LMP is found in higher plasma concentrations than the parent drug in patients and one can expect similar success or superior results in achieving the desired serotonergic antagonist effects as that of LMP.

Claims 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morel et al. (Psychopharmacology, 1987, 92, 68-72) as applied to claims 1, 4 above and in view of Hals et al. (Life Sciences, 43, 405-412, 1988).

Morel et al's teachings discussed as above.

The reference does not teach the administration of NDM-LMP to a patient a pharmaceutically acceptable formulation with reduced α adrenergic antagonist effect and reduced histaminic antagonist effects relative to administering levomepromazine.

Hals et al. teaches that NDM-LMP has relatively high affinity for histamine H1 receptors as well as α1 adrenoreceptors that have been proposed to be involved in mediating sedative effects of neuroleptics (p 409, lines 39-42).

It would have been obvious to one of ordinary skill in the art at the time of invention to adjust the dose range of NDM-LMP by routine experimentation to achieve reduced α adrenergic antagonist effect and reduced histaminic antagonist effects relative to administering levomepromazine. Morel teaches a dose of LMP and NDM-LMP that produces half maximal response when administered to rats. Hence it would have been obvious to one of ordinary skill in the art to test various dosages of NDM-LMP with respect to LMP by routine experimentation to achieve the desired effects of sedation or hypotension.

The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." I*n re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Conclusion

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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SUPERVISOR